

REVIEW ARTICLE

Impact of Glycemic Control on Healthcare Resource Utilization and Costs of Type 2 Diabetes: Current and Future Pharmacologic Approaches to Improving Outcomes

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Background: The incidence and prevalence of type 2 diabetes continue to grow in the United States and worldwide, along with the growing prevalence of obesity. Patients with type 2 diabetes are at greater risk for comorbid cardiovascular (CV) disease (CVD), which dramatically affects overall healthcare costs.

Objectives: To review the impact of glycemic control and medication adherence on morbidity, mortality, and healthcare costs of patients with type 2 diabetes, and to highlight the need for new drug therapies to improve outcomes in this patient population.

Methods: This comprehensive literature search was conducted for the period between 2000 and 2013, using MEDLINE, to identify published articles that report the associations between glycemic control, medication adherence, CV morbidity and mortality, and healthcare utilization and costs. Search terms included “type 2 diabetes,” “adherence,” “compliance,” “nonadherence,” “drug therapy,” “resource use,” “cost,” and “cost-effectiveness.”

Discussion: Despite improvements in the management of CV risk factors in patients with type 2 diabetes, outcomes remain poor. The costs associated with the management of type 2 diabetes are increasing dramatically as the prevalence of the disease increases. Medication adherence to long-term drug therapy remains poor in patients with type 2 diabetes and contributes to poor glycemic control in this patient population, increased healthcare resource utilization and increased costs, as well as increased rates of comorbid CVD and mortality. Furthermore, poor adherence to established evidence-based guidelines for type 2 diabetes, including underdiagnosis and undertreatment, contributes to poor outcomes. New approaches to the treatment of patients with type 2 diabetes currently in development have the potential to improve medication adherence and consequently glycemic control, which in turn will help to reduce associated costs and healthcare utilization.

Conclusions: As the prevalence of type 2 diabetes and its associated comorbidities grows, healthcare costs will continue to increase, indicating a need for better approaches to achieve glycemic control and manage comorbid conditions. Drug therapies are needed that enhance patient adherence and persistence levels far above levels reported with currently available drugs. Improvements in adherence to treatment guidelines and greater rates of lifestyle modifications also are needed. A serious unmet need exists for greatly improved patient outcomes, more effective and more tolerable drugs, as well as marked improvements in adherence to treatment guidelines and drug therapy to positively impact healthcare costs and resource use.

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The incidence and prevalence of type 2 diabetes continue to grow in the United States as the population ages and becomes more obese.^{1,2} The

prevalence of type 2 diabetes is projected to increase from current estimates of 14% to at least 21% of the US population by 2050, but the prevalence rate could reach 33% of the population.³

The impact of weight on the prevalence of type 2 diabetes is dramatic. In the 1999-2002 National Health and Nutrition Examination Survey (NHANES), among patients with type 2 diabetes, the proportion of partici-

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pants who were overweight (ie, body mass index [BMI] ≥ 25 kg/m²) or obese (ie, BMI ≥ 30 kg/m²) was 85.2%, and the proportion of obese patients without diabetes was 54.8% (**Figure 1**).¹ Obese patients with type 2 diabetes were characterized by younger age, poorer glycemic control, higher blood pressure, worse lipid profile, and use of antihypertensive and lipid-lowering drugs compared with their nondiabetic counterparts.

Patients with diabetes are at greater risk for microvascular and macrovascular disease, including coronary artery disease, stroke, peripheral vascular disease, end-stage renal disease, retinopathy, and mortality, compared with persons without diabetes.⁴ Large-scale studies in patients with diabetes consistently report a direct association between lower hemoglobin (Hb) A_{1c} levels and lower complication rates.⁵⁻⁷

The proportion of the national healthcare expenditure attributed to patients with type 2 diabetes is expected to increase from the reported 10% in 2011 to 15% by 2031.⁸ In addition, studies show that overall healthcare costs for type 2 diabetes are reduced with improved glycemic control in patients with diabetes.⁹⁻¹¹ Improvements in the management of type 2 diabetes and weight control, which are linked to increased medication adherence, are a critical component of any effort to reduce the healthcare costs of type 2 diabetes.

An unmet need in the treatment of type 2 diabetes is the availability of effective, safe, and well-tolerated treatments that will achieve and maintain glycemic control, reduce body weight, and decrease cardiovascular (CV) risk, while also ensuring patient adherence and persistence with therapy.

This article provides a comprehensive review of the impact of type 2 diabetes on patient morbidity and mortality, the implications of and increased prevalence of type 2 diabetes and its associated comorbidities on the costs of healthcare, and potential new pharmacologic approaches to control the prevalence of disease and their associated costs. For the purposes of this review, comprehensive searches were conducted for the years 2000 to 2013 using MEDLINE for individual and combinations of search terms, including “type 2 diabetes,” “adherence,” “compliance,” “nonadherence,” “drug therapy,” “resource use,” “cost,” and “cost-effectiveness.” Articles in the English language and representing healthcare practices in the United States were selected for inclusion.

Impact of Type 2 Diabetes on Morbidity and Mortality

Despite improvements in the management of CV risk factors in patients with type 2 diabetes in recent years, substantial proportions of patients remain with elevated HbA_{1c} (29%-45%), blood pressure (49%), and low-density lipoprotein cholesterol (LDL-C; 47%) according

KEY POINTS

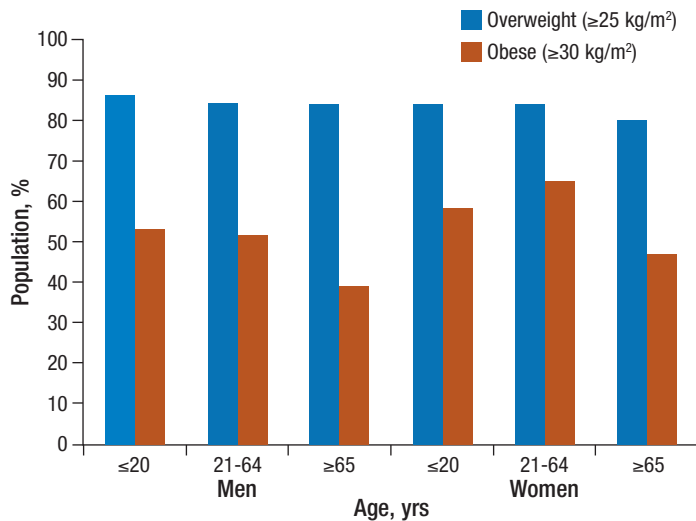
- Despite improvements in the management of patients with type 2 diabetes and associated cardiovascular risk factors, patient adherence and outcomes remain poor.
- The costs associated with this disease are increasing dramatically as its prevalence increases; estimates of the economic burden of diabetes in 2007 reached \$153 billion and are estimated to increase 3-fold in the next 20 years.
- Improved glycemic control in patients with type 2 diabetes has been shown to improve outcomes and reduce overall costs.
- Important unmet needs include lack of medication adherence and suboptimal use of evidence-based guidelines and lifestyle modifications, resulting in poor outcomes.
- This retrospective literature review of type 2 diabetes highlights the urgent need to improve the approach to drug therapy to control glycemic levels, improve the associated cardiovascular morbidity and mortality, and reduce obesity and overall costs.
- A review of novel therapies currently in development suggests the potential for new approaches to drug therapies that may help to improve glycemic control, improve outcomes, and reduce costs in patients with type 2 diabetes.
- The authors call for therapies that will focus on patient convenience and increased safety to enhance medication adherence and reduce morbidity and mortality far beyond the levels reported with current medications.

to NHANES data.^{12,13} As the prevalence of type 2 diabetes grows, a parallel increase in comorbidity and mortality can be expected.^{2,14,15}

The incidence of CV disease (CVD) is markedly exacerbated by poor glycemic control in patients with type 2 diabetes.^{16,17} Increased rates of hypertension, dyslipidemia, heart failure, angina, and myocardial infarction are closely linked to poor glycemic control in type 2 diabetes.⁶ Microvascular complications also are affected by poor glycemic control.⁶ An analysis of the UKPDS study showed a significant association between HbA_{1c} levels and the risk for microvascular complications.⁷ Each 1% reduction in mean HbA_{1c} was associated with a 21% reduction in the risk of any adverse outcome and a 37% reduction in the risk of microvascular complications.⁷ An HbA_{1c} reduction from 8% to <7%, and the associated reductions in risk, would result in savings for

Figure 1

Proportion of Type 2 Diabetic Men and Women Who Were Overweight or Obese in the NHANES Database, 1999-2002, by Age



NHANES indicates National Health and Nutrition Examination Survey.

Source: Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep.* 2004;53:1066-1068.

hospitalization from diabetes of \$486 per patient per year, with even greater cost reductions when comparing higher HbA_{1c} levels with HbA_{1c} levels <7%.¹⁸

Currently available hypoglycemic drugs demonstrate limited effects on CV risk factors beyond glycemic control.¹⁹ Development of CVD is a major complication of type 2 diabetes. Chronic hyperglycemia is often accompanied by dyslipidemia, hypertension, systemic inflammation, and oxidative stress, which increase the risk for microvascular and macrovascular complications of type 2 diabetes.¹⁹ Although metformin exhibits favorable effects on body weight, sulfonylureas, thiazolidinediones, and insulin have a negative impact on weight in patients with type 2 diabetes.²⁰

Glucagon-like peptide (GLP)-1 receptor agonists enhance insulin secretion but may also exert effects beyond glycemic control. Ongoing studies are examining the effects of administering GLP-1 agonists to patients at risk for CVD, patients postangioplasty, patients post-coronary artery bypass, and patients with heart failure.²¹ Additional studies are evaluating the potential benefits on arrhythmias, heart failure, myocardial infarction, and death.^{22,23}

Implications of Growing Prevalence of Type 2 Diabetes and Comorbidities on Healthcare Costs

Despite current availability of a wide range of drugs for the management of patients with type 2 diabetes, a number of limitations associated with their use persist, such as

suboptimal efficacy, poor weight control, tolerability concerns, and high rates of medication nonadherence. In addition, suboptimal control of comorbid conditions, including hypertension and dyslipidemia, are common.²⁴

Data from NHANES were examined to assess the achievement of therapeutic targets for glycemic control, blood pressure, and LDL-C among patients with diabetes in the United States.²⁵ The proportion of patients with diabetes achieving HbA_{1c} levels <7%, blood pressure <130/80 mm Hg, and LDL-C <100 mg/dL had risen from 7% during 1999-2002 to 12.2% during 2003-2006, but this increased rate represents a striking indication of the need for greater efforts to manage diabetes and its comorbidities.²⁵

The costs associated with the management of patients with type 2 diabetes are increasing dramatically as the prevalence of the disease increases.²⁶ Estimates of the economic burden of diabetes in the United States in 2007 reached \$153 billion in excess medical costs and \$65 billion in lost productivity.²⁶ Healthcare expenditures associated with type 2 diabetes are expected to increase approximately 3-fold during the next 20 years,² and additional costs are projected to arise from poor adherence to drug therapy.^{27,28}

Obstacles to Effective Management of Type 2 Diabetes

Despite the availability of therapies to improve glycemic control and reduce the associated comorbidities, medication adherence and long-term persistence with long-term drug therapy remains inadequate. This level of poor adherence is estimated to account for 33% to 69% of hospital admissions in the United States.²⁹ Causes of poor adherence include complex drug regimens, chronic disease, adverse effects, cost, poor communication between patients and providers, lack of symptomatology, and psychosocial issues such as lack of education and support for behavioral modification.²⁹

From a payer perspective, this gap between investing in programs and therapies needs to be addressed to avoid consequences that may not be seen for decades for a patient who is not a member of the specific health plan. Furthermore, the conundrum of covering weight-loss medications needs to be evaluated. Many health plans do not cover weight-loss medications, despite the association between obesity, diabetes, and CVD, because of concerns of cost, adverse plan selection, and poor sustained efficacy and tolerability of weight-loss agents.

Medication adherence to different classes of antidiabetic drugs was evaluated from pharmacy claims for 75,589 patients enrolled in 3 health plans over a 12-month period in 2003, and average medication nonadherence was approximately 31% (range, 25%-55%).³⁰ A systematic review of adherence to the prescribed dose of

antidiabetic drugs showed adherence rates from 67% to 85% for oral drugs and from 62% to 64% for insulin.³¹ In contrast, diabetic patients using subcutaneous injection of insulin were found adherent in only 36.1% of cases before conversion to an insulin pen device (which led to 54.6% adherence).³² An analysis of therapy with GLP-1 agonists between 2005 and 2010 showed adherence rates of 31% to 34%, suggesting that the need for injection even at a weekly frequency is a barrier to adherence.³³

A 2005 analysis of persistence with drug therapy for 6 chronic diseases showed 6-month persistence rates of 28% to 66%.³⁴ For diabetes, hypertension, and dyslipidemia, the medication possession ratio (MPR) averaged 72%, but only 59% of patients were adherent to their medication for >80% of the days, annually.³⁵ Medication adherence refers to the intensity of drug use during therapy, whereas persistence refers to the overall duration of drug therapy; therefore, a patient can have poor adherence (eg, does not take medication as prescribed) but a high persistence rate (or MPR), because the patient continues to take the medication long-term.³⁶

Improving medication adherence offers the possibility of reducing costs and improving care for patients with a chronic illness. A 2010 analysis of nonadherence (ie, MPR <80%) to medications used to treat diabetes, dyslipidemia, or hypertension estimated that the direct cost of nonadherence was \$105.8 billion in that year.²⁷ In addition, the CVS Caremark pharmacy and administrative claims database was used to determine the effect of medication adherence from 2005 to 2008 on healthcare costs, including hospital days, emergency department visits, and outpatient visits.³⁷ Based on this analysis, greater medication adherence was projected to reduce the average annual medical spending per patient with diabetes by \$4413 for all adults and by \$5170 for patients aged ≥65 years.³⁷

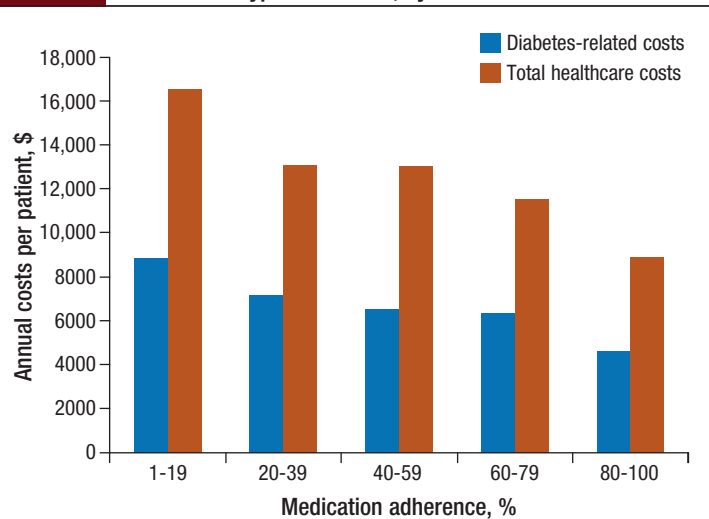
Adherence and Healthcare Resource Use

Poor medication adherence in patients with diabetes is associated with poor glycemic control, which ultimately increases morbidity and mortality and further impacts healthcare costs.^{38,43} Extensive data exist that link poor medication adherence to increased medical resource use and higher healthcare costs in type 2 diabetes. Improved medication adherence may lead to reductions of the total healthcare costs in type 2 diabetes.

A systematic literature review investigated the economic impact of adherence and/or persistence with treatment on the overall cost of type 2 diabetes care.³⁸ The average total annual costs per patient ranged from \$4570 to \$17,338. Medication adherence was inversely associated with total healthcare costs or hospitalization costs.³⁸

In a population of patients with diabetes examined

Figure 2 Annual Diabetes-Related and Total Healthcare Costs per Patient with Type 2 Diabetes, by Medication Adherence Level



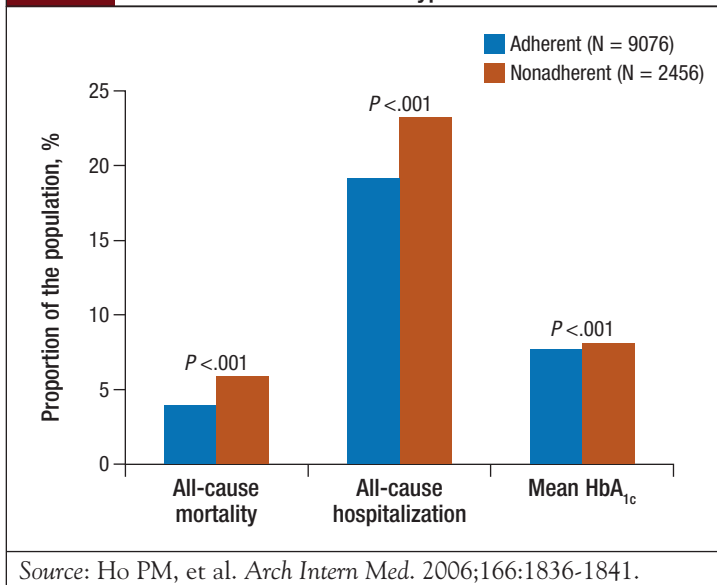
Source: Sokol MC, et al. *Med Care*. 2005;43:521-530.

from 2005 to 2008, improved adherence to diabetes medications was associated with a 13% reduction in the risk of hospitalization or emergency department visits, whereas poor adherence was associated with a 15% increase in risk.⁴¹ Based on these findings, adherence to diabetes medication was projected to save \$4.7 billion annually, and eliminating poor adherence would save the US healthcare system \$3.6 billion annually.⁴¹ Thus, improved medication adherence among diabetic patients has the potential for a significant impact on costs.

A retrospective analysis using an administrative claims database of 137,277 patients enrolled in a healthcare system from June 1997 to May 1999 was performed to determine the impact of adherence (percentage of days that a patient had a supply of medication) on hospitalization rates and costs related to diabetes, hypertension, congestive heart failure, and hypercholesterolemia.⁴² For patients with diabetes, a significant increase in adherence rates was associated with reductions in hospitalization risk from 30% to 13% ($P < .05$) and total costs (ie, medical and drug costs) increased from \$8867 to \$4570 ($P < .05$) over a 12-month period (Figure 2).⁴²

A model that was created to estimate the impact of medication adherence in 56,744 patients with type 2 diabetes who were enrolled in private insurance plans from 2001 to 2002 showed that increasing medication adherence (using MPR) from 50% to 100% would reduce the hospitalization rate from 15% to 11.5% and emergency department visits from 17.3% to 9.3%.⁴⁴ The cost to achieve this level of adherence was projected to be an increase of \$776 annually per patient, but this added cost was projected to be offset by cost-savings from lower rates

Figure 3 Unadjusted Association for All-Cause Mortality, All-Cause Hospitalization, and Mean HbA_{1c} Level in Adherent/Nonadherent Patients with Type 2 Diabetes



of hospitalization and emergency department visits, which were estimated at \$886 per patient annually.⁴⁴

A longitudinal study from 2002 to 2006 evaluated medication adherence in patients with type 2 diabetes and the cost benefits of improving adherence.³⁹ The mean MPR over 5 years was 0.93 for the adherent group and 0.58 for the nonadherent group. The costs increased approximately 3% annually ($P = .001$) during the 5-year study period. Nonadherence was associated with a 37% lower pharmacy cost and a 7% lower outpatient cost, but a 41% higher inpatient cost. Improving adherence in the nonadherent group was projected to result in annual cost-savings in the range of \$661 million to \$1.16 billion.³⁹

A retrospective, cross-sectional study evaluated the effect of adherence to antidiabetic medications on adherence rates, healthcare utilization, and work productivity.⁴⁰ Patients with type 2 diabetes using oral antidiabetic medications with or without insulin ($N = 96,734$) and patients using oral medication only ($N = 55,356$) were evaluated. Adherence (ie, MPR >80%) was associated with fewer complications of diabetes and fewer emergency department visits and short-term disability days. Among patients taking oral antidiabetic medications only, adherence was associated with significantly lower rates of acute myocardial infarction, amputation, neuropathy, renal events, and retinopathy ($P < .05$).⁴⁰

The impact of increased persistency with medication use on hospitalization rates and healthcare costs was evaluated in 7441 Medicare patients with type 2 diabetes between 1997 and 2004 using prescription data to estimate

costs.⁴³ Persistency with prescriptions for oral antidiabetic medications, antihypertensives, and statins was associated with a significantly lower risk of hospitalization, fewer hospital days, and lower healthcare costs ($P < .05$).

Adherence and Glycemic Control

The impact of medication adherence on glycemic control in type 2 diabetes has been evaluated in a number of prospective and retrospective studies.

The effect of adherence on glycemic control was evaluated in 249 patients in a managed care plan who had recently initiated therapy with oral antidiabetic drugs between 2001 and 2004.⁴⁵ Overall, mean adherence (MPR >80%) was 81%, and older age and comorbidity were associated with better adherence. Each 10% increase in adherence was associated with a 0.1% reduction in HbA_{1c} ($P = .004$), and adherent patients were more likely to achieve glycemic control.

A retrospective study was conducted between 1991 and 2001 among 1560 patients with type 2 diabetes to determine the effect of medication adherence with oral drugs on glycemic control measured by HbA_{1c} during a 1-year follow-up.⁴⁶ After adjusting for age, sex, BMI, and other factors, glycemic control rates improved progressively in accordance with higher rates of medication adherence. HbA_{1c} levels were 0.34% lower with improvements in medication adherence ($P = .009$).

The effect of medication adherence on glycemic control was also evaluated in a retrospective analysis of patients with type 2 diabetes enrolled in an independent practice association model HMO between 2001 and 2002.⁴⁷ The HbA_{1c} target of $\leq 7\%$ was achieved by 42% to 46% of patients using oral antidiabetic drugs. The mean MPR for patients who reached HbA_{1c} goal versus patients who did not reach that goal was 0.82 and 0.72 for sulfonylureas and 0.77 and 0.62 for metformin ($P < .001$). An inverse relationship was observed between mean HbA_{1c} level and MPR.⁴⁷

Adherence and Mortality

Poor medication adherence also is associated with an increase in mortality in type 2 diabetes. A retrospective cohort study was conducted between 2002 and 2005 to investigate the effects of poor adherence on hospitalization and mortality in 11,532 patients with type 2 diabetes in a managed care organization.³⁶ Medication adherence was defined as the proportion of days covered for filled prescriptions of oral hypoglycemic, antihypertensive, and statin medications. Patients who were nonadherent had higher levels of HbA_{1c}, blood pressure, and LDL-C. Medication nonadherence was significantly ($P < .001$) associated with an increased risk for all-cause hospitalization and for all-cause mortality (Figure 3).³⁶

An analysis of the association between medication adherence and mortality in patients with type 2 diabetes found that medication nonadherence and clinic non-attendance were independent risk factors for all-cause mortality.⁴⁸ Data were obtained from general practices in the United Kingdom for 15,984 patients with type 2 diabetes who were treated with an oral antidiabetic drug and insulin. Medication nonadherence was significantly more common in women, smokers, and those with a higher HbA_{1c}.⁴⁸

Glycemic Control and Healthcare Resource Use

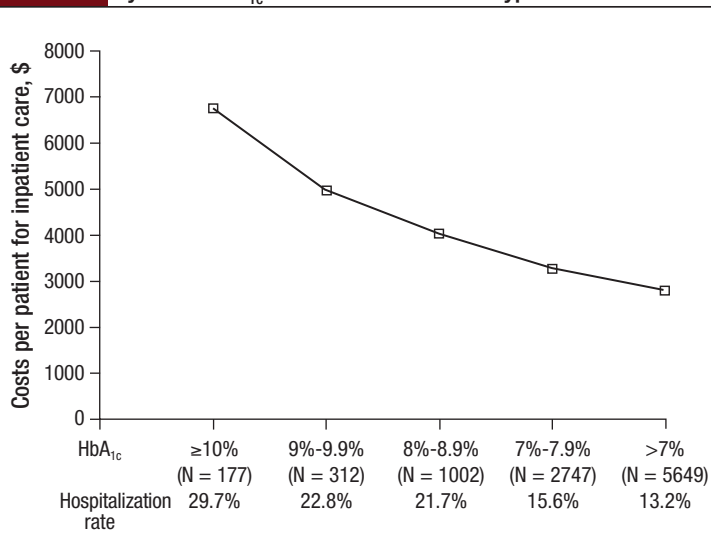
A strong association has been reported between poor glycemic control in type 2 diabetes and healthcare resource use and costs. A retrospective analysis from a managed care organization evaluated the relationship between glycemic control and hospitalization rate and hospital costs among patients with type 1 or type 2 diabetes.¹⁸ The hospitalization rate was significantly higher among patients with an HbA_{1c} $\geq 10\%$ compared with patients with HbA_{1c} $< 7\%$ ($P < .05$). Average costs per patient increased markedly from \$2792 to \$6759 over a 40-month period that coincided with increasing HbA_{1c} values (Figure 4).¹⁸

An administrative database from a healthcare plan was used to assess the effects of glycemic control on healthcare costs between 1998 and 2003 among 10,780 patients with type 2 diabetes.⁴⁹ Total annual diabetes-related costs increased significantly ($P < .05$) from \$1505 among patients with good glycemic control (HbA_{1c} $\leq 7\%$) to \$1871 among patients with poor control (HbA_{1c} $> 9\%$).⁴⁹ Among members of a managed care plan with type 2 diabetes who maintained HbA_{1c} levels $\leq 7\%$ during a 1-year follow-up in 2002, diabetes-related costs were significantly reduced.¹⁰ This retrospective analysis compared medical and pharmacy claims data for 3121 patients at target HbA_{1c} levels and for 3659 patients above target. At a 1-year follow-up, average diabetes-related costs per patient were \$1540 for the cohort with high HbA_{1c} levels versus \$1171 for the group at target HbA_{1c} ($P < .001$). These results demonstrate that higher medical costs associated with type 2 diabetes management are linked to poor glycemic control.¹⁰

Effect of Comorbidity on Healthcare Resource Use

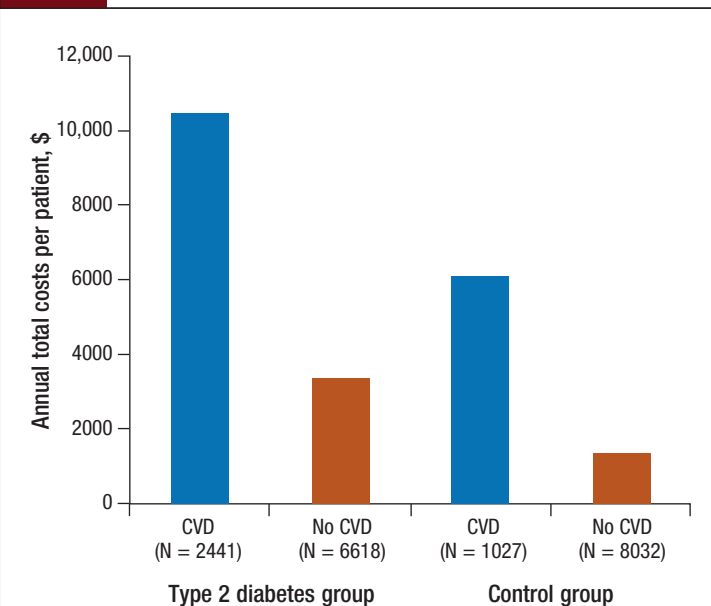
In addition to the effects of type 2 diabetes on costs and resource utilization, the presence of underlying CVD magnifies the costs of care. The effect of comorbid CVD on healthcare costs was evaluated in patients with type 2 diabetes enrolled in an HMO in 2003.⁵⁰ Costs were compared in 9059 patients with type 2 diabetes and age-matched controls. Total healthcare costs were 3-fold higher in patients with comorbid CVD versus patients without comorbidities, which was similar to the control

Figure 4 Cost per Patient for Inpatient Care and Hospitalization Rate, by Mean HbA_{1c} Level in Patients with Type 2 Diabetes



Source: Menzin J, et al. *J Manag Care Pharm.* 2010;16:264-275.

Figure 5 Annual Total Cost per Patient with/without Type 2 Diabetes and with/without CVD



CVD indicates cardiovascular disease.

Source: Gandra SR, et al. *J Manag Care Pharm.* 2006;12:546-554.

group of persons without type 2 diabetes (Figure 5). However, the total costs were approximately 2-fold higher in patients with type 2 diabetes, regardless of the presence of comorbid CVD.⁵⁰

An economic benefit from weight loss was demonstrated among patients with type 2 diabetes, especially

among obese patients. The impact of weight change over 1 year was evaluated using a claims database among adults in an HMO between 1997 and 2005.²⁰ Of the 458 patients included, 224 (48.9%) experienced weight gain of ≤ 1 lb. The average 1-year healthcare cost was \$6382 per person, and the diabetes-related cost was \$2002. For patients who gained weight (mean, 3.9%) during the 1-year follow-up, the average healthcare cost was \$7260 per person, and the diabetes-related cost was \$2141. For those with no change in weight (mean, 3.3% decrease), the average healthcare cost was \$5541 per person and the average diabetes-related cost was \$1869.²⁰ Therefore, a 1% weight loss was associated with a significant 3.6% (\$256) decrease in total healthcare cost and a 5.8% (\$131) decrease in diabetes-related cost ($P < .05$).²⁰

Unmet Needs and Future Directions in Drug Therapy for Type 2 Diabetes

There remain unmet needs for better pharmacologic treatment of type 2 diabetes. The ideal therapy should halt disease progression, reduce CV complications, and have a benign safety and tolerability profile. Optimal therapy requires continuous control of glucose levels and a more intensive therapeutic effect to prevent or reduce glucose excursions.⁵¹ Progress toward developing new therapies for type 2 diabetes that satisfy the ideal profile is limited by the complex nature of diabetes and its effects on multiple organ systems, as well as the length of time required for symptoms to develop.

The goal is for effective, safe, and well-tolerated treatments that will achieve glycemic control and ensure adherence and persistence with therapy. Ideal treatments should provide additional benefits beyond glycemic control, such as significant effects on weight loss and CV risk factors (including blood pressure and lipids), with an expectation of reduced morbidity and mortality. In addition, ideal therapies will lack the inconvenience and barriers associated with frequent injections, offer patient convenience, and optimize medication adherence. An important treatment approach to type 2 diabetes that has the potential to improve adherence and disease outcomes is the use of dual- or triple-drug combination therapy.

Treatment guidelines for type 2 diabetes include recommendations for using combination therapy, and a growing body of literature supports the early use of triple-drug therapy for patients who are not adequately controlled with monotherapy.⁵²⁻⁵⁴

A number of fixed-dose combinations of antidiabetic drugs are already marketed or are undergoing clinical evaluation. Finally, healthcare payers expect that ideal therapies will provide cost-effective solutions to the long-term management of type 2 diabetes to address the high morbidity and costs associated with CVD.

Novel approaches for improving pharmacotherapy for type 2 diabetes include new delivery systems for existing drugs and new chemical entities, as outlined in the **Table**, based on ongoing clinical trials (clinicaltrials.gov; accessed July 16, 2013). Many of the new classes of drugs target comorbid CVD in patients with type 2 diabetes.

Although a once-weekly formulation of exenatide (Bydureon; Amylin) is available and other once-weekly formulations of GLP-1 receptor agonists are in development and a once-monthly formulation is undergoing evaluation, the impact of these agents on long-term adherence remains uncertain.

New formulations of older drugs are focused on improved delivery of the active ingredient to provide increased ease of use and patient convenience. ITCA 650 (Intarcia Therapeutics) is a novel drug delivery system that is designed to provide continuous subcutaneous release of exenatide for up to 1 year. Phase 3 trials are under way in patients with type 2 diabetes to demonstrate its efficacy and tolerability.

A once-monthly suspension of exenatide (Bristol-Myers Squibb) has completed a phase 2 trial and is poised to enter phase 3 studies. Oral formulations of GLP-1 receptor agonists are in early clinical testing.

Inhaled insulin (Afrezza; MannKind Corporation) is an ultra-rapid-acting inhaled formulation that is intended as an alternative to rapid-acting injectable insulin and offers the major advantage of avoiding frequent daily injections. Additional phase 3 studies are being conducted for submission to the US Food and Drug Administration (Exubera was withdrawn from the market by its manufacturer in 2008).

Another approach to addressing unmet needs in type 2 diabetes is drug combinations that provide 2 mechanisms of action. The dipeptidyl peptidase-4 agonist alogliptin combined with pioglitazone (Oseni; Takeda Pharmaceuticals) and alogliptin combined with metformin (Kazano; Takeda Pharmaceuticals) were both approved and launched early in 2013, and insulin degludec combined with liraglutide is in late-stage development (Novo Nordisk).

Furthermore, the cost-effectiveness of fixed-dose combinations must be demonstrated in diabetes, especially when ≥ 1 of the components are available as generic drugs, and when patients are likely taking multiple medications. There is a need to establish a direct link between improved medication adherence and better outcomes.

A number of new chemical entities for type 2 diabetes are in clinical development or have recently been added to the market. The first sodium-glucose cotransporter (SGLT)2, canagliflozin (Invokana; Janssen), was approved and launched in early 2013. Other SGLT2 compounds are in late-stage development, and these agents

Table Novel Drugs in Late-Stage Development for the Treatment of Type 2 Diabetes

Drug/novel delivery system (company)	Description	Novel features	Development stage
ITCA 650 (Intarcia Therapeutics)	Novel delivery system of exenatide, GLP-1 receptor agonist	Continuous delivery for up to 12 mo with 1 insertion	Phase 3
Inhaled insulin (MannKind)	Short-acting insulin (new version of Exubera, which was withdrawn from the market in 2008)	Inhaled to avoid need for frequent self-injection	Phase 3
Exenatide monthly (Bristol-Myers Squibb/Amylin)	GLP-1 receptor agonist	Less frequent than currently available versions of exenatide (ie, monthly injection)	Phase 2
Combination drug			
Insulin degludec + liraglutide (Novo Nordisk)	Long-acting insulin + GLP-1 receptor agonist	Exogenous insulin to augment insulin secretion	Phase 3
New chemical entities			
SGLT2 inhibitors (Astra Zeneca/Bristol-Myers Squibb) (Boehringer Ingelheim/Lilly)	SGLT2	Increases secretion of urinary glucose; low risk of hypoglycemia, weight loss, and blood pressure reduction	Phase 3
Ipragliflozin (Astellas Pharma)			Phase 3
Empagliflozin + simvastatin (Boehringer Ingelheim/Lilly)	SGLT2 + statin	Increases secretion of urinary glucose; low risk of hypoglycemia, weight loss, and blood pressure reduction combined with lipid-lowering properties	Phase 3
Dual SGLT1 and SGLT2 inhibitor (Lexicon)	Dual inhibition of SGLT2	Oral administration; inhibits gastrointestinal glucose absorption and renal reabsorption	Phase 3
DGAT1 inhibitor: LCQ908 (Novartis Pharmaceuticals)	Acyl-CoA:DGAT 1 inhibitor	Reduces insulin resistance and triglycerides without TZD side effects	Phase 2
<p>NOTE: This list is not inclusive. Rather, it is focused on products that represent a novel approach to therapy, including (1) novel delivery systems, (2) novel drugs; or (3) novel combinations that are in late-stage development (ie, phase 3 or late stage 2 clinical trials).</p> <p>DGAT indicates diacylglycerol acyltransferase; GLP-1, glucagon-like peptide-1; SGLT, sodium glucose cotransporter; TZD, thiazolidinedione.</p> <p>Source: Clinicaltrials.gov, searched using the terms “phase 2,” “phase 3,” “industry sponsored,” and “type 2 diabetes,” focusing on novel features only (ie, delivery system, drug class, or drug combinations). Accessed July 16, 2013.</p>			

increase secretion of urinary glucose and promote weight loss, with a low risk for hypoglycemia or blood pressure reduction. A dual SGLT1 and SGLT2 agonist that inhibits glucose absorption in the stomach and renal glucose reabsorption is in phase 3 development (Lexicon Pharmaceuticals).

G protein-coupled receptor agonists act as incretin mimetics (CymaBay), and acyl-CoA:diacylglycerol acyltransferase 1 (DGAT1) inhibitors are being developed by various manufacturers (Novartis; Pfizer) to reduce insulin resistance and lower triglycerides. These drug classes are in early-stage development.

Alternative approaches to treatment are in early clinical development and include drugs that reduce glycemia

while providing beta-cell protection (GMC-252; Genmedica Therapeutics), selective inhibition of proinflammatory pathways, and activation of endogenous anti-inflammatory pathways (CAT-1004; Catabasis). More effective weight-loss agents are needed, and healthcare plans need better tools to validate the return-on-investment to employers for treating obesity.

Conclusions

The information presented in this article should serve as a call to action for health insurance plans, pharmacy benefit managers, and employers to investigate the impact of medication adherence on costs and outcomes associated with type 2 diabetes. Greater effort is needed

from these groups to assess the level of medication adherence, as well as adherence to evidence-based guidelines and connect potential improvements to quality measures in type 2 diabetes. With continuing growth in the prevalence of type 2 diabetes, its associated comorbidities, and a corresponding increase in healthcare costs, it is critical that better approaches are identified for achieving long-term glycemic control and managing comorbid conditions.

A major emphasis should be placed on achieving effective control of diabetes, but without imposing increased risks on the patient from excess weight, hypoglycemia, and other safety and tolerability concerns. Of equal importance is to find drug therapies that increase patient adherence and persistence levels beyond levels reported with currently available drugs. This combination of enhanced efficacy, better tolerability, and improved adherence has the potential to impart substantial positive benefits on healthcare costs and resource utilization and ensure a healthier population. New Centers for Medicare & Medicaid Services' Clinical Quality Measures⁵⁵ that are linking reimbursement to the attainment of quality measures may provide additional incentive to improving overall management of type 2 diabetes and its comorbidities. ■

Author Disclosure Statement

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STAKEHOLDER PERSPECTIVE

Innovation in Patient Engagement and Management Is Critically Needed to Change Current Trends in Type 2 Diabetes

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PAYERS: Payers are challenged with how to use limited healthcare resources to produce quality outcomes in a healthcare system that many believe is fragmented and inefficient. One of the most challenging areas is the management of patients with type 2 diabetes mellitus. In their article in this issue of *American Health & Drug Benefits*, Drs Banerji and Dunn aptly make the case for a call to action for aggressive change and innovation in the management of patients with type 2 diabetes and the development of new pharmaceuticals that reduce cardiovascular risk, result in less weight gain, and improve adherence and health outcomes. This need is reflected in the heavy weighting of specific diabetes quality measures in the new Centers for Medicare & Medicaid Services Medicare Part C & D Plan Ratings Quality and Performance Measures for diabetes care.¹ The aging of our population, alarming increases in obesity, poor diets, and inadequate exercise contribute to the diabetes healthcare epidemic that, if unabated, will negatively impact healthcare costs, morbidity, and mortality.

As the authors point out, the issues are complex, but there are potential short-term strategies that payers could consider to address this growing concern. Increasing member personal accountability for health and med-

ication management through incentives and disincentives that promote behavioral change in adherence, diet, and exercise could lead to meaningful improvements in patient adherence, glycemic control, health outcomes, and cost reduction. Application of proven high-touch, high-technology models for patient care delivery that have been successful in managing patients with other complex medical conditions could help.

The specialty pharmacy model has successfully achieved medication adherence rates in excess of 90% with many complex diseases. Their care management and data capture capabilities, patient and provider interaction, and scalability warrant serious consideration of this model for improvements in adherence and outcomes. Payer collaboration with the pharmaceutical industry to develop and evaluate effective formal patient education programs is also needed. Programs that adapt existing multimedia and interactive technologies that measure learning and comprehension about the potential benefits and potential risks of their medications in the context of their medical condition could contribute to gaps in medication education. Payer incentives for members who complete formal education could ensure that all patients with diabetes are appropriately educated

STAKEHOLDER PERSPECTIVE *Continued*

on the pharmacologic and nonpharmacologic components of their treatment plan.

PATIENTS: The authors provide a loud wake-up call for patients with type 2 diabetes and persons with risk factors for the disease regarding the projected increases in healthcare costs, obesity, morbidity, and mortality that are related to diabetes. This information should be conveyed to patients to encourage changes in their personal lifestyles and adherence to their provider's treatment plan, to be used as the rationale for introducing positive and negative incentives to drive individual member behavior.

PROVIDERS: Drs Banerji and Dunn document ongoing issues of poor adherence and treatment outcomes despite improvements in care delivery. This has not gone unrecognized by the federal government and quality organizations that are influencing the shift in accountability to healthcare providers for performance on quality measures that will include incentives and disincentives that are linked to reimbursement. Provider adoption of electronic medical records will also provide new opportunities for diabetes care management and for the reporting that is critical to the success of accountable care organizations in addressing diabetes quality measures.

Providers will need to play an increasing role in improving patient education and reinforcement of behaviors that are critical to treatment adherence and to

medication safe use and management, which for many practices has been a challenge because of time constraints, patient health literacy, complex medication regimens, and the lack of effective tools that they can deploy in their practices.

PHARMACEUTICAL COMPANIES: The authors appropriately introduce the need for additional drug development for therapies that effectively provide glycemic control without weight gain, that are convenient to use by patients, and that lead to high medication adherence rates in real-world clinical practices. Combination therapies that reduce "pill burden" are promising, as are new therapies with novel mechanisms of action and drug delivery systems that are designed to reduce weight gain and to improve medication adherence.

The pharmaceutical industry should consider collaborating with payers, providers, and patients to assess the impact of new therapies and collaborative care delivery models on medication adherence, outcomes, and healthcare costs and utilization. The development of comprehensive, effective patient medication education programs that address healthcare literacy and the multicultural educational needs of patients with diabetes by leveraging consumer and provider market research on gaps in education are urgently needed.

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